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Dalcetrapib

JTT 705; JTT-705; R 1658; R1658; RG1658; RO 4607381; RO4607381

Abstract

Roche and Japan Tobacco are in a licensing agreement to develop and commercialize dalcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor to slow or prevent atherosclerosis. This drug is currently in phase III development. This review discusses the development history and scientific profile of this new compound.

1. Introduction

Dalcetrapib, a thioester, is a cholesteryl ester transfer protein (CETP) inhibitor that is being developed by Roche and Japan Tobacco to slow or prevent atherosclerosis. CETP is a plasma glycoprotein that mediates the transfer of cholesteryl ester from high-density lipoprotein (HDL)-cholesterol to proatherogenic very low-density lipoprotein (VLDL)-cholesterol and low-density lipoprotein (LDL). Dalcetrapib is in phase III trials worldwide and in a phase II trial in Japan for the treatment of hyperlipidemia (dyslipidemia).

1.1 Company Agreements

In October 2004, Japan Tobacco and Roche entered into a licensing agreement for the development and commercialization of dalcetrapib. Japan Tobacco was to retain rights in Japan and Korea, and receive milestone payments and royalties from Roche for exclusive rights in the rest of the world.[1] It appears that the agreement was amended to list only Japan as the excluded territory.

1.2 Key Development Milestones

In April 2008, Roche began a phase III study to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality in stable coronary heart disease patients with recent Acute Coronary Syndrome (ACS) and evaluate the long-term safety profile of the drug (NCT00658515). Enrollment of approximately 15 600 patients has been completed from sites around the world and patients are randomized to receive either dalcetrapib 600 mg or placebo daily, together with stable medication for ACS.[2] Completion of this study is expected in April 2013. The company reported in March 2010 that enrollment in the phase III trial was continuing and that regulatory submissions for dalcetrapib for the treatment of atherosclerosis in high-risk patients with cardiovascular disorders are planned for 2013.[3]

Favorable safety and efficacy results were reported from phase II trials of dalcetrapib in patients with dyslipidemia, coronary heart disease (CHD), or CHD risk equivalents with type 2 diabetes mellitus and/or metabolic syndrome.[4,5]

A phase II trial (NCT00655473) is evaluating the effect of dalcetrapib on progression or regression of atherosclerotic plaque in patients with coronary heart disease and with other CHD risk factors. This study involves 100 patients in the US and Canada who are receiving dalcetrapib 600 mg or placebo daily for 24 months. Roche expects this study to reach completion in 2011. Another phase II trial (NCT00655538) is assessing the safety, tolerability and effect on endothelial function of dalcetrapib in patients with CHD or CHD risk equivalents. Patients were randomized to receive dalcetrapib 600 mg or placebo for 36 weeks. Enrollment of 476 patients was completed in March 2010, in Europe. Completion of this study is anticipated in January 2011.

Roche initiated phase II US development of dalcetrapib in 100-500 patients with dyslipidemia in 2005. The double-blind, multicenter, parallel, randomized study examined the effect of dalcetrapib in combination with pravastatin on HDL-cholesterol levels in patients with low or average HDL-cholesterol levels (NCT00697203). The trial also examined apolipoprotein A1, LDL-cholesterol, total cholesterol and triglyceride levels. Roche has published positive phase II efficacy data.[6]

Dalcetrapib is in phase II development in Japan for the treatment of hyperlipidemia, according to the Japan Tobacco pipeline dated May 2009.

2. Scientific Summary

2.1 Adverse Events

2.1.1 Hyperlipidemia

Phase II: Data from phase II trials of dalcetrapib alone (at doses up to 900 mg/day) or in combination with HMG-CoA reductase inhibitors (statins) have shown that dalcetrapib was generally well tolerated in patients with type II hyperlipidemia, CHD or CHD risk equivalents, with a similar incidence of adverse events (AEs) and serious AEs seen in dalcetrapib and placebo recipients. Pooled data were analyzed from four, double-blind, placebo-controlled, phase IIa trials conducted in 546 patients who received dalcetrapib 300 mg, 600 mg or 900 mg monotherapy (one study) for 4 weeks, or combination treatment with dalcetrapib 300 mg or 600 mg in combination with a statin (three studies). In a separate analysis, safety data from a 12-week, phase IIb combination study of dalcetrapib 300 mg, 600 mg or 900 mg with pravastatin (n = 218) versus placebo treatment (n = 74) were evaluated. In the phase IIa trials, all AEs were mild to moderate in intensity with the most frequent AEs reported being gastrointestinal disorders (i.e. diarrhea [6.3–10%], flatulence [4–6.3%], nausea [1.4–6.6%]), headache (2.9–10.4%) and dizziness (4.2–6%). In the phase IIb trials, the most frequent AEs included diarrhea (6.6–10.3%), upper respiratory tract infection (2.6–5.4%), stomach discomfort (1.3–2.9%) and myalgia (muscle pain; 1.3–4.1%).[7,8]

Dalcetrapib at dosages of 300, 600 and 900 mg/day, was well tolerated in patients with hyperlipidemia. Digestive complaints occurred in 21%, 25% and 27% of 300, 600 and 900 mg/day recipients, and 12% of placebo recipients.[9]

Twenty-four-week treatment with dalcetrapib (900 mg daily) was well tolerated in patients with

Table I. Features and properties

Alternate names	JTT 705; JTT-705; R 1658; R1658; RG1658; RO 4607381; RO4607381
Originator	Japan Tobacco
Licensee(s)	Roche
Highest development phase	III (World)
Active development-indications	Hyperlipidemia
Class	Small-molecules, Sulfhydryl-compounds
Mechanism of action	Cholesterol ester transfer protein inhibitors
Chemical name	*S*- [2- [[[1-(2-ethylbutyl)cyclohexyl] carbonyl] amino] phenyl] propanethioic acid, 2-methy-,
Molecular formula	C23 H36 N O2 S
CAS registry number	211513-37-0
Route of administration	PO
Pharmacodynamics	Increases high-density lipoprotein cholesterol and decreases cholesteryl ester transfer protein activity in patients with hyperlipidemia; attenuates atherosclerosis in cholesterol-fed rabbits
ATC codes	
WHO ATC code	C10A (Lipid Modifying Agents, Plain)
EphMRA ATC code	C10A9 (All other cholesterol/triglyceride regulators)
Adverse events	
Most frequent	Diarrhea, Gastrointestinal disorders, Headache
Occasional	Dizziness, Flatulence, Muscle pain, Nausea, Respiratory tract infections

Table II. History

Date	Comment
8 April 2010	inThought analysis for hyperlipidemia updated
19 February 2010	Roche completes enrollment in its phase III trial for hyperlipidemia in multiple countries around the world
15 February 2010	Roche completes enrollment in a phase II trial for hyperlipidemia in Europe
2 October 2009	Efficacy and adverse events data from phase II trials in patients with dyslipidemia, coronary heart disease (CHD), or CHD risk equivalents presented at the 45th Annual Meeting of the European Association for the Study of Diabetes (EASD-2009)[4,5]
1 May 2008	Phase II clinical trials in hyperlipidemia in Japan (PO)
16 April 2008	Phase III clinical trials in hyperlipidemia in world excluding Japan (PO)
1 April 2008	Adverse events data from phase II trials in patients with type II hyperlipidemia, coronary heart disease (CHD), or CHD risk equivalents presented at the 57th Annual Scientific Session of the American College of Cardiology (ACC-2008)[7,8]
1 June 2007	Dalcetrapib is still in phase II trials for hyperlipidemia
27 April 2007	Phase I clinical trials in hyperlipidemia in Japan (PO)
1 March 2007	No development reported – phase I for hyperlipidemia in Japan (PO)
1 July 2005	Phase II clinical trials in hyperlipidemia in the US (PO)
26 October 2004	JTT 705 has been licensed to Roche worldwide excluding Japan and Korea
10 March 2003	A clinical study has been added to the adverse events and hyperlipidemia pharmacodynamics sections[9]
26 April 2002	Phase II clinical trials in hyperlipidemia in the Netherlands (PO)
1 November 2000	Phase II clinical trials for hyperlipidemia (unknown route)
1 November 2000	Phase I clinical trials for hyperlipidemia in Japan (unknown route)
1 November 2000	New profile

dyslipidemia, CHD or CHD risk equivalents with and without type 2 diabetes and/or metabolic syndrome (T2DM/MetSyn). In the study, 107 patients with T2DM/MetSyn received dalcetrapib (n = 74) or placebo (n = 33) and 28 patients without T2DM/MetSyn received dalcetrapib (n = 15) or placebo (n = 13) for 24 weeks. By week 24, 82% (n = 61) of dalcetrapib recipients and 82% (n = 27) of placebo recipients in the T2DM/MetSyn group reported ≥1 AE. In patients without T2DM/MetSyn, AEs were reported in 87% (n = 13) and 77% (n = 10) of dalcetrapib and placebo recipients, respectively. Most AEs were mild to moderate in intensity and considered unrelated to dalcetrapib. The most common AEs, occurring in ≥10% of patients in those with T2DM/MetSyn, were upper respiratory tract infection (URTI [15%/9%]) and diarrhea (14%/12%), for dalcetrapib/placebo recipients, respectively. The most common AEs, occurring in ≥10% of patients in those without T2DM/MetSyn, were URTI (13%/23%), diarrhea (20%/8%), flatulence (7%/23%) and nasopharyngitis (7%/15%) for dalcetrapib/placebo recipients, respectively. No effect on blood pressure, fasting glucose or glycosylated hemoglobin (HbA_{1C}) was observed. Serious AEs occurred in 8% (n = 6) and 6% (n = 2) of dalcetrapib and placebo recipients, respectively, in the T2DM/MetSyn group. Serious AEs were reported in 20% (n = 3) and 15% (n = 2) of patients in those without T2DM/MetSyn. No serious AE was considered related to treatment. The tolerability profile was sustained for up to 48 weeks.[4]

2.2 Pharmacodynamics

2.2.1 Hyperlipidemia

Clinical studies: After 4 weeks, dalcetrapib at dosages of 300, 600 and 900 mg/day, had increased HDL-cholesterol levels ($p \leq 0.001$), and decreased cholesteryl ester transfer protein activity ($p \leq 0.001$) in patients with hyperlipidemia.[9]

Preclinical studies: Dalcetrapib attenuated atherosclerosis in cholesterol-fed rabbits according to the results of a study conducted in Japan. In this study, rabbits were given a cholesterol-containing diet alone to establish hyperlipidemia, then dalcetrapib or simvastatin was added

Table III. Forecasts

InThought Probability of Approval			
Indication	Approval Date Estimate	InThought Approvability Index	Last Update
Hyperlipidemia	5 Oct 2013	50%	8 Apr 2010

to the diet for 6 months. Compared with untreated controls, dalcetrapib and simvastatin recipients had HDL-cholesterol levels, which were 90% and 28% higher, respectively, and non-HDL-cholesterol levels which were 40–50% and 50–70% lower, respectively. Compared with controls, the area of atherosclerotic lesions in the aortic arch was 70% lower in dalcetrapib recipients and 80% lower in simvastatin recipients. [10]

Dalcetrapib demonstrated 95% inhibition of cholesteryl ester transfer protein, a protein that transfers neutral lipids among lipoproteins, in JW rabbits.[11]

2.3 Therapeutic Trials

2.3.1 Hyperlipidemia

Post hoc analysis of data from four phase II trials in patients with dyslipidemia, CHD or CHD risk equivalents with and without type 2 diabetes and/or metabolic syndrome (T2DM/MetSyn) showed that dalcetrapib 600 mg had comparable efficacy in patients with and without T2DM and/or MetSyn. In the studies, 296 patients with T2DM/MetSyn received dalcetrapib 600 mg (n = 124) or placebo (n = 172) and 192 patients without T2DM/MetSyn received dalcetrapib 600 mg (n = 90) or placebo (n = 102) for 4 weeks. In the T2DM/MetSyn group, significant increases from baseline at 4 weeks in key parameters were reported with dalcetrapib versus placebo recipients (HDL-cholesterol [+24.0], apolipoprotein A-I [+10.2], apolipoprotein B [+4.4] and total cholesterol [+6.6]). A significant reduction in CETP activity was reported (−11.1) with dalcetrapib treatment in this group. In those without T2DM/MetSyn, significant increases from baseline at 4 weeks in HDL-cholesterol [+26.4] and apolipoprotein A-I [+10.7] were reported with dalcetrapib versus placebo recipients. Significant reductions in ApoB : ApoA-I (−11.8) and CETP activity (−10.0) were reported with dalcetrapib treatment in this group. In either patient group, no significant change in triglyceride level was observed.[5]

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